WRITTEN OPINION

Form PCT/IPEA/408 (Box V) (January 1994)
FILE COPY - DO NOT MAIL

International application No.
PCT/US98/11312

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	1-23	YES
	Claims	none	NO
Inventive Step (IS)	Claims	1-23	YES
	Claims	none	NO
Industrial Applicability (IA)	Claims	1-23	YES
	Claims	none	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-23 meet the criteria set out in PCT Article 33(2)-(4), because the prior art teaches only a 2-carboxy-quinoline substituted with 4-amino (NICHOLS et al.) or 4-sulfonimide (HARRISON et al. 5606063), does not teach or fairly suggest the instant N,N-diphenyl-4-ureido on the quinoline. The instant invention finds industrial applicability as an agent for treating withdrawal syndromes or for treating neuroexcitability disorders.

---------- NEW CITATIONS ----------

NONE

WRITTEN OPINION

Form PCT/IPEA/408 (Box VII) (January 1994)
FILE COPY - DO NOT MAIL

International application No.

PCT/US98/11312

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

The description is objected to as containing the following defect(s) under PCT Rule 66.2(a)(iii) in the form or contents thereof: in the structural formula I on page 11 of the disclosure, does applicant intend R2 and R3 to be attached to a nitrogen (as indicated in compounds 6, 7 of page 18) instead of a carbon as shown?

WRITTEN OPINION

Form PCT/IPEA/408 (Box VIII) (January 1994)
FILE COPY - DO NOT MAIL

International application No.

PCT/US98/11312

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 11, 12, 16, 17, 22, 23 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not adequately described in writing, as required under PCT Rule 5.1(a)(iii), for the reasons set forth in the immediately preceding paragraph. The N,N-diphenyl-4-ureido compounds of claims 11, 16, 17, 22, 23 have no antecedent basis in the base claims 1 or 12. Further, in formula I, it is unclear how R2, R3 with the intervening carbon form a carbonyl, thiocarbonyl, imino etc.

TO:	UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)
TALIVALDIS CEPURITIS OLSON & HIERL, LTD. 20 NORTH WACKER DRIVE, 36TH FLOOR CHICAGO, IL 60606	**NOTIFICATION OF STATUS OF REQUIREMENTS UNDER 35 U.S.C. 371**
	DATE OF MAILING *(day/month/year)* 30 JUN 98
	FILE REFERENCE TBK-102-PCT

IDENTIFICATION OF INTERNATIONAL APPLICATION

International application No.	International filing date *(day/month/year)*	Priority Date Claimed
PCT/US98/11312	05 JUN 98	06 JUN 97

Applicant for DO/EO/US

TABAKOFF, BORIS

NOTIFICATION

The applicant is hereby advised that the U.S. Patent and Trademark Office in its capacity as [X] Designated Office [ ] Elected Office has received following items as of the date of mailing indicated above.

1. [ ] U.S. Nation fee [35 U.S.C 371 (c) (1)]
2. [ ] Oath of declaration [35 U.S.C 371 (c) (4)]
3. [X] Copy of International application as [35 U.S.C 371 (c) (2)]
4. [ ] Translation of Application [35 U.S.C 371 (c) (2)]
5. [ ] Amendments under PCT Article 19 [35 U.S.C 371 (c) (3)]
6. [ ] Translation of PCT Article 19 Amendments [35 U.S.C 371 (c) (3)]
7. [ ] Search Report or Declaration under PCT Article 17(2) [35 U.S.C 371 (a)]
8. [ ] International Preliminary Examination Report and its Annexes, if any, under PCT Article 36(3)(b) [35 U.S.C 371 (a)]
9. [ ] Translation of Annexs to the International Preliminary Examination Report under PCT Article 36(3)(b) [35 U.S.C 371 (c) (5)]
10. [ ] Other items received:
    - [ ] Assignment Document
    - [ ] Prior Art Statement
    - [ ] Preliminary Amendment

A. [ ] Requirements for U.S. National processing have been met. Processing will commence
- [ ] at the expiration of the applicable time limit under either
  - [ ] PCT Article 22 [35 U.S.C 371 (b)] or
  - [ ] PCT Article 39 [35 U.S.C 371 (b)]
- [ ] on the date indicated below under the provisions of 35 U.S.C 371 (f)

U.S. NATIONAL SERIAL#	DATE UNDER 35 U.S.C. 102(e)	DATE OF COMMENCEMENT OF NATIONAL PROCESSING

All correspondence submitted after the date of commencement of U.S. National processing indicated above should refer to the U.S. National Serial Number and the appropriate U.S. National processing organization of Officer.

B. [ ] As the above identified application has been accepted for U.S. National processing under the provision of 35 U.S.C.371 (f) before expiration of the applicable time limit under [ ] PCT Article 22 [ ] PCT Article 39, applicant is reminded that
- [ ] Amendments under PCT Article 19 and/or
- [ ] the International Preliminary Examination Report and its Annexes, if any, under PCT Article 36(3) (a), and (b) and any translation thereof, if applicable, must be submitted to the Patent and Trademark Office as soon as they are available.

International application No.	International filing date	Priority Date Claimed
PCT/US98/11312	05 JUN 98	06 JUN 97

C. [X] In order that U.S. National processing may begin, certain items must be received by the DO/EO/US by the expiration of applicable time limit under

- [ ] PCT Article 22 or
- [ ] PCT Article 39.

Specifically:

- [X] 1. U.S. National Fee
- [X] 2. Oath or Declaration
- [ ] 3. Copy of Application
- [ ] 4. Translation of application
- [X] 5. Amendments under PCT Article 19, if any
- [ ] 6. Translation of PCT Article 19 Amendments, if applicable
- [ ] 7. Search Report or PCT Article 17(2) declaration
- [ ] 8. International Preliminary Examination Report and its Annexes, if any, under PCT Article 36(3)(a), if applicable
- [ ] 9. Translation of Annexs to the International Preliminary Examination Report under PCT Article 36(3)(b), if appliable

THE ABOVE CHECK ITEMS MUST BE TIMELY RECEIVED TO AVOID ABANDONMENT OF THE APPLICATION. [35. U.S.C. 371(d)]

D. Further information for the applicant:

This is only a reminder.

UNITED STATES DESIGNATED/ELECTED OFFICE

Address Only:	Authorized Office
Assistant Commissioner for Patent Box PCT Washington, D.C. 20231 Attn:RO/US	Virginia L. Irby V L Irby

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference TBK-102-PCT	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US98/11312	International filing date *(day/month/year)* 05 JUNE 1998	(Earliest) Priority Date 06 JUNE 1997
Applicant LOHOCLA RESEARCH CORPORATION		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (See Box I).

2. [ ] **Unity of invention is lacking** (See Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] transcribed by this Authority.

4. With regard to the title,
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the abstract,
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is:

   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/11312

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/47; C07D 215/48
US CL :514/313; 546/159, 163

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/313; 546/159, 163

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,493,027 A (NICHOLS et al.) 20 February 1996, see entire document, especially columns 17-18, claim 1.	1-22
A	US 5,026,700 A (HARRISON et al.) 25 June 1991, see entire document, especially columns 23-24, claim 1 and column 26, claims 32-43.	1-22
A	US 5,606,063 A (HARRISON et al.) 25 February 1997, columns 1-2.	1-22

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 29 JULY 1998	Date of mailing of the international search report 03 SEP 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer EVELYN HUANG Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)★

09/171697

PCT/US98/11312

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 09 February 1999 (09.02.99)	
International application No. PCT/US98/11312	**Applicant's or agent's file reference** TBK-102-PCT
International filing date (day/month/year) 05 June 1998 (05.06.98)	**Priority date** (day/month/year) 06 June 1997 (06.06.97)
Applicant TABAKOFF, Boris et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   29 December 1998 (29.12.98)

   [ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Athina Nickitas-Etienne
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

2469145

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :		(11) International Publication Number:
A61K 31/47, C07D 215/48	A1	WO 98/55125
		(43) International Publication Date: 10 December 1998 (10.12.98)

(21) International Application Number: PCT/US98/11312

(22) International Filing Date: 5 June 1998 (05.06.98)

(30) Priority Data:
60/048,848 6 June 1997 (06.06.97) US

(71) Applicant *(for all designated States except US)*: LOHOCLA RESEARCH CORPORATION [US/US]; 1200 Olive Street, Denver, CO 80220 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: TABAKOFF, Boris [US/US]; 1352 East Schappville Road, Elizabeth, IL 61028 (US). SNELL, Lawrence [US/US]; 1565 South Paris Court, Aurora, CO 80012 (US). HOFFMAN, Paula, L. [US/US]; 1633 Ivanhoe, Denver, CO 80220 (US).

(74) Agents: CEPURITIS, Talivaldis et al.; Olson & Hierl, Ltd., 36th floor, 20 North Wacker Drive, Chicago, IL 60606 (US).

(81) Designated States: AU, CA, JP, MX, RU, US, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: COMPOUNDS, COMPOSITIONS AND METHOD SUITABLE FOR AMELIORATION OF WITHDRAWAL SYNDROMES AND WITHDRAWAL–INDUCED BRAIN DAMAGE

(57) Abstract

Compounds, compositions and method for ameliorating alcohol or drug dependency withdrawal syndromes and withdrawal–induced brain damage are disclosed. In particular, a series of N–substituted–4–ureido–5,7–dihalo–2–carboxy quinoline compounds are disclosed having combined properties as antagonists of voltage–sensitive sodium channels (VSNaC) and as selective competitive antagonists at the strychnine–intensive glycine site of N–methyl–D–aspartate (NMDA) receptors. The disclosed compounds prevent or reduce the signs and symptoms of neurohyperexcitability and particularly the neurohyperexcitability associated with withdrawal syndrome manifested by patients upon withdrawal from chronic use of dependence inducing agents (e.g, ethanol, barbiturates, opiates etc.). The combined actions of the disclosed compounds on VSNaC and NMDA receptors also impart properties to these compounds that are important in preventing and reducing excitotoxic neurodegeneration and reducing anxiety without the undesirable CNS depressant side–effects of agents hitherto employed for these purposes.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/11312

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 31/47; C07D 215/48
US CL :514/313; 546/159, 163
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/313; 546/159, 163

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,493,027 A (NICHOLS et al.) 20 February 1996, see entire document, especially columns 17-18, claim 1.	1-22
A	US 5,026,700 A (HARRISON et al.) 25 June 1991, see entire document, especially columns 23-24, claim 1 and column 26, claims 32-43.	1-22
A	US 5,606,063 A (HARRISON et al.) 25 February 1997, columns 1-2.	1-22

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"B"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 29 JULY 1998	Date of mailing of the international search report 03 SEP 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer EVELYN HUANG Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

PATENT COOPERATION TREATY

PCT

1663 INTERNATIONAL PRELIMINARY EXAMINATION REPORT

09/171697

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference TBK-102-PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US98/11312	International filing date *(day/month/year)* 05 JUNE 1998	Priority date *(day/month/year)* 06 JUNE 1997
International Patent Classification (IPC) or national classification and IPC IPC(6): A61K 31/47; C07D 215/48 and US Cl.: 514/313; 546/159, 163		
Applicant LOHOCLA RESEARCH CORPORATION		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 8 sheets.

3. This report contains indications relating to the following items:

- I [X] Basis of the report
- II [ ] Priority
- III [ ] Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV [ ] Lack of unity of invention
- V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI [ ] Certain documents cited
- VII [ ] Certain defects in the international application
- VIII [X] Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29 DECEMBER 1998	13 AUGUST 1999
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer EVELYN HUANG Telephone No. (703) 308-1235

JOYCE BRIDGERS
PARALEGAL SPECIALIST
CHEMICAL MATRIX

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US98/11312

I. Basis of the report

1. This report has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments)*:

☐ the international application as originally filed.

☒ the description, pages (See Attached) , as originally filed.
pages _____ , filed with the demand.
pages _____ , filed with the letter of _____.
pages _____ , filed with the letter of _____.

☒ the claims, Nos. (See Attached) , as originally filed.
Nos. _____ , as amended under Article 19.
Nos. _____ , filed with the demand.
Nos. _____ , filed with the letter of _____.
Nos. _____ , filed with the letter of _____.

☒ the drawings, sheets/~~fig~~ (See Attached) , as originally filed.
sheets/~~fig~~ _____ , filed with the demand.
sheets/~~fig~~ _____ , filed with the letter of _____.
sheets/~~fig~~ _____ , filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☒ the description, pages NONE.
☒ the claims, Nos. NONE.
☒ the drawings, sheets/~~fig~~ NONE.

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US98/11312

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	1-23	YES
	Claims	none	NO
Inventive Step (IS)	Claims	1-23	YES
	Claims	none	NO
Industrial Applicability (IA)	Claims	1-23	YES
	Claims	none	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-23 meet the criteria set out in PCT Article 33(2)-(4), because the prior art teaches only a 2-carboxy-quinoline substituted with 4-amino (NICHOLS et al.) or 4-sulfonimide (HARRISON et al. 5,606,063), does not teach or fairly suggest the instant N,N-diphenyl-4-ureido on the quinoline. The instant invention finds industrial applicability as an agent for treating withdrawal syndromes or for treating neuroexcitability disorders.

---------- NEW CITATIONS ----------
NONE

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 11, 12, 16, 17, 22, 23 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not adequately described in writing, as required under PCT Rule 5.1(a)(iii), for the reasons set forth in the following paragraph.

In formula I, it is still unclear how R2, R3 with the intervening nitrogen and carbon form a carbonyl, thiocarbonyl, imino etc.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

I. BASIS OF REPORT:

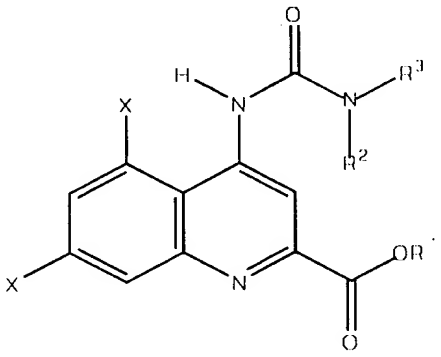
This report has been drawn on the basis of the description,
pages, 1-7, 10 and 13-41, as originally filed.
pages, NONE, filed with the demand.
and additional amendments:
Pages 8, 9, 11, 12, filed with the letter of 14 June 1999.

This report has been drawn on the basis of the claims,
numbers, 17-23, as originally filed.
numbers, NONE, as amended under Article 19.
numbers, NONE, filed with the demand.
and additional amendments:
Claims 1-16 filed with the letter of 14 June 1999.

This report has been drawn on the basis of the drawings,
sheets, 1-13, as originally filed.
sheets, NONE, filed with the demand.
and additional amendments:
NONE

withdrawal or withdrawal-induced brain damage manifested in a patient suffering withdrawal symptoms is disclosed. The term "withdrawal syndromes" as used herein includes, but is not limited to, manifestations of one or more symptoms of CNS hyperexcitability associated with alcohol withdrawal syndromes, neuroexcitability disorders associated with drug withdrawal syndromes, neural brain damage induced by alcohol or drug dependence withdrawal and like neurodegenerative disorders associated with chronic drug use and withdrawal.

A preferred method comprises administering a physiologically effective amount of a compound having the general formula (I):



(I)

a tautomer thereof, a pharmacologically acceptable ester, amide, salt, ether, or an acid addition salt thereof;

wherein R^1 represents hydrogen or an alkyl group of 1 to 6 carbon atoms;

R^2 and R^3 each independently represent phenyl which may be unsubstituted or substituted one or more times with substituents selected from the group consisting of alkoxy, cycloalkoxy, alkyl, and cycloalkyl groups containing up to 6 carbon atoms, hydrogen, hydrocarbon selected from the group consisting of straight chain, branched, cyclic, and heterocyclic groups containing up to 18 carbon atoms, halogen, cyano, trifluoromethyl, nitro, $-OR^a$, $-SR^a$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-NR^aSO_2R^b$, $-NR^iCZNR^aR^b$, $-CO_2$, or $-CONR^aR^b$; wherein R^a, R^b, R^i each independently represent hydrogen or hydrocarbon as described above and can be the same or different and Z represents oxygen,

sulphur, or a group of formula =N,E; wherein E represents hydrocarbon as described above or an electron-withdrawing group; or

R^2 and R^3 together with the intervening nitrogen and carbon atom represent carbonyl (C=O), thiocarbonyl (C=S), imino (C=N,R^a), oximino (C=N,OR^a), or a 3- to 8-membered ring containing from zero to 4 hetero-atoms selected from the group consisting of oxygen, nitrogen, sulphur and phosphorus; wherein R^a represents hydrogen or hydrocarbon as described above;

wherein each of the R^2 and R^3 substituents can be the same or different; and

X represents halogen and each of the 5, 7, substituents can be the same or different.

Administration of the compound can be by oral, intravenous, subcutaneous, intramuscular, intraperitoneal, transdermal or buccal means for therapeutic treatment.

Preferred compounds of the general formula (I) are N-substituted 4-ureido-5,7-dihalo-2-carboxy quinoline compounds. Particularly preferred compounds were derivatives of kynurenic acid, hereafter referred to generally as DCUK compounds. Presently preferred DCUK compounds are (N,N-diphenyl)-4-ureido-5,7-dichloro-2-carboxy-quinoline (DCUKA); (N,N-diphenyl)-4-ureido-5,7-dichloro-2-carboxy-quinoline methyl ester)(DCUK-OMe); and N-phenyl, N-[2-methoxy]phenyl)-4-ureido-5,7-dichloro-2-carboxy-quinoline (MeO-DCUKA) which demonstrate affinity for both the strychnine-insensitive glycine binding site on the NMDA receptor complex and voltage-sensitive sodium channels.

The inventive DCUK compounds beneficially possess activity in reducing drug withdrawal-induced and excitotoxin-induced CNS hyperexcitability and neuronal damage at doses devoid of CNS depressant effects. Even at high doses, the DCUK compounds efficiently inhibit, in a use dependent manner, voltage sensitive sodium channels and inhibit NMDA receptor function without inducing the adverse marked behavioral stimulation and ataxia effects associated with known NMDA receptor antagonists or voltage sensitive sodium channel blockers. Additionally, the inventive DCUK compounds beneficially reduce or prevent in vitro measures of glutamate excitotoxicity.

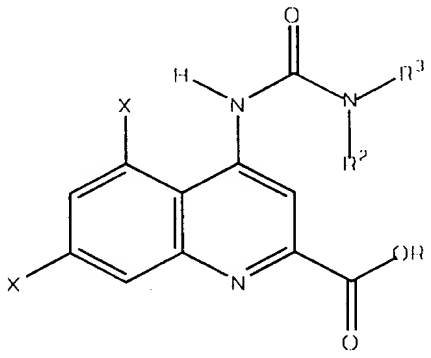
FIG. 13 shows the effects of (±)HA-966 on rotarod performance in naive C57BL/6 mice.

Detailed Description of Preferred Embodiment

Disclosed are compounds, compositions and a method suitable for treating dependence on, or preventing the withdrawal syndrome from being manifested during withdrawal from, the chronic use of ethanol, or other sedative or hypnotic or analgesic drugs in a patient (humans or other mammalian animal species). Withdrawal syndrome manifestations include, but are not limited to CNS hyperexcitability, such as tremors, insomnia, anorexia, disorientation, seizures, convulsions, anxiety or the like. The present compounds, compositions and method also provide for treating neurodegenerative disorders associated with chronic drug use and withdrawal induced brain damage.

The method provided by the present invention comprises administering by systemic means to a patient in need of such treatment or prevention an effective ameliorating amount of a compound which exhibits both an affinity for the strychnine-insensitive glycine binding site on the NMDA receptor complex and affinity for voltage-sensitive sodium channels (VSNaC).

A preferred compound embodiment has the general formula (I):



(I)

a tautomer thereof, a pharmacologically acceptable ester, amide, salt, ether, or an acid addition salt thereof;

wherein R^1 represents hydrogen or an alkyl group of 1 to 6 carbon atoms;

R^2 and R^3 each independently represent phenyl which may be unsubstituted or substituted one or more times with substituents selected from the group consisting of alkoxy, cycloalkoxy, alkyl, and cycloalkyl groups containing up to 6 carbon atoms, hydrogen, hydrocarbon selected from the group consisting of straight chain, branched, cyclic, and heterocyclic groups containing up to 18 carbon atoms, halogen, cyano, trifluoromethyl, nitro, $-OR^a$, $-SR^a$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-NR^aSO_2R^b$, $-NR^iCZNR^aR^b$, $-CO_2$, or $-CONR^aR^b$; wherein R^a, R^b, R^i each independently represent hydrogen or hydrocarbon as described above and can be the same or different and Z represents oxygen, sulphur, or a group of formula $=N,E$; wherein E represents hydrocarbon as described above or an electron-withdrawing group; or

R^2 and R^3 together with the intervening nitrogen and carbon atom represent carbonyl (C=O), thiocarbonyl (C=S), imino ($C=N,R^a$), oximino ($C=N,OR^a$), or a 3- to 8-membered ring containing from zero to 4 hetero-atoms selected from the group consisting of oxygen, nitrogen, sulphur and phosphorus; wherein R^a represents hydrogen or hydrocarbon as described above;

wherein each of the R^2 and R^3 substituents can be the same or different; and

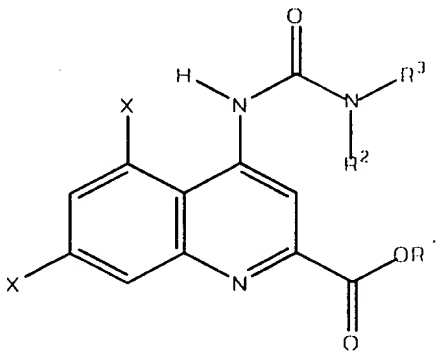
X represents halogen and each of the 5, 7, substituents can be the same or different.

The term "alkyl" as used herein refers to lower alkyl groups containing less than 7 carbon atoms. A preferred alkyl group has 1 to 3 carbon atoms. The term "hydrocarbon" as used herein includes straight-chained, branched, and cyclic groups, including heterocyclic groups, containing up to 18 carbon atoms, suitably up to 15 carbon atoms, and conveniently up to 12 carbon atoms. The term "halogen" as used herein includes chloro, fluoro, bromo and iodo substituents, preferably chloro. The term "alkoxy" as used herein refers to alkoxy groups containing less than 7 carbon atoms, preferably 1 to 3 carbon atoms. The term "substituted phenyl" refers to phenyl having one or more substituents selected from the group consisting of alkoxy, cycloalkoxy, alkyl, and

CLAIMS

WE CLAIM:

1. A method suitable for treating withdrawal syndromes manifested in a patient suffering withdrawal symptoms and/or withdrawal-induced brain damage which comprises administering an effective ameliorating amount of a compound having the general formula (I):



(I)

a tautomer thereof, a pharmacologically acceptable ester, amide, salt, ether, or an acid addition salt thereof;

wherein R^1 represents hydrogen or an alkyl group of 1 to 6 carbon atoms;

R^2 and R^3 each independently represent phenyl which may be unsubstituted or substituted one or more times with substituents selected from the group consisting of alkoxy, cycloalkoxy, alkyl, and cycloalkyl groups containing up to 6 carbon atoms, hydrogen, hydrocarbon selected from the group consisting of straight chain, branched, cyclic, and heterocyclic groups containing up to 18 carbon atoms, halogen, cyano, trifluoromethyl, nitro, $-OR^a$, $-SR^a$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-NR^aSO_2R^b$, $-NR^iCZNR^aR^b$, $-CO_2$, or $-CONR^aR^b$; wherein R^a, R^b, R^i each independently represent hydrogen or hydrocarbon as described above and can be the same or different and Z represents oxygen, sulphur, or a group of formula $=N,E$; wherein E represents hydrocarbon as described above or an electron-withdrawing group; or

R^2 and R^3 together with the intervening nitrogen and carbon atom represent carbonyl (C=O), thiocarbonyl (C=S), imino (C=N,R^a), oximino (C=N,OR^a), or a 3- to 8-membered ring containing from zero to 4 hetero-atoms

selected from the group consisting of oxygen, nitrogen, sulphur and phosphorus; wherein R^a represents hydrogen or hydrocarbon as described above;

wherein each of the R^2 and R^3 substituents can be the same or different; and

X represents halogen and each of the 5, 7, substituents can be the same or different.

2. The method of claim 1 wherein in the compound of formula (I) each of the X substituents is chloro, R^1 is hydrogen, and R^2 and R^3 each is a phenyl group.

3. The method of claim 1 wherein in the compound of formula (I) each of the X substituents is chloro, R^1 is an alkyl group having 1 to 3 carbon atoms, and R^2 and R^3 each is a phenyl group.

4. The method of claim 1 wherein in the compound of formula (I) each of the X substituents is chloro, R^1 is hydrogen, one of R^2 and R^3 is an unsubstituted phenyl group and the other is phenyl having an alkoxy substituent having 1 to 3 carbon atoms.

5. The method of claim 1 wherein the treatment is for alcohol withdrawal.

6. The method of claim 1 wherein the treatment is for drug withdrawal.

7. The method of claim 1 wherein the treatment is for withdrawal-induced brain damage.

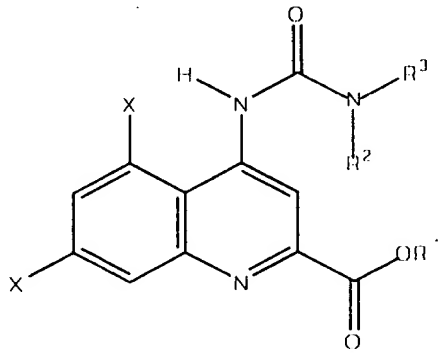
8. The method of claim 1 wherein the compound is administered in an amount of up to about 500 mg/kg of body weight.

9. The method of claim 1 wherein the amount of compound administered is in the range of about 10 to about 100 mg/kg of body weight.

10. A composition suitable for use in the method of claim 1 containing a compound selected from the group consisting of a compound of formula (I), a tautomer, or pharmaceutically acceptable ester, amide, salt, ether and addition salt thereof, in an amount of about 0.1 to about 95 weight percent and a pharmaceutically acceptable vehicle.

11. The composition of claim 10 wherein the compound is selected from the group consisting of (N,N-diphenyl)-4-ureido-5,7-dichloro-2-carboxy-quinoline, (N,N-diphenyl)-4-ureido-5,7-dichloro-2-carboxy-quinoline methyl ester, and N-phenyl, N-[2-methoxy]phenyl)-4-ureido-5,7-dichloro-2-carboxy-quinoline.

12. A compound suitable for treating withdrawal syndromes manifested in a patient suffering withdrawal symptoms and/or withdrawal-induced brain damage which comprises administering an effective ameliorating amount of a compound having the general formula (I):



(I)

a tautomer thereof, a pharmacologically acceptable ester, amide, salt, ether, or an acid addition salt thereof;

wherein R^1 represents hydrogen or an alkyl group of 1 to 6 carbon atoms;

R^2 and R^3 each independently represent phenyl which may be unsubstituted or substituted one or more times with substituents selected from the group consisting of alkoxy, cycloalkoxy, alkyl, and cycloalkyl groups containing up to 6 carbon atoms, hydrogen, hydrocarbon selected from the group consisting of straight chain, branched, cyclic, and heterocyclic groups containing up to 18 carbon atoms, halogen, cyano, trifluoromethyl, nitro, $-OR^a$, $-SR^a$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-NR^aSO_2R^b$, $-NR^iCZNR^aR^b$, $-CO_2$, or $-CONR^aR^b$;

wherein R^a, R^b, R^i each independently represent hydrogen or hydrocarbon as described above and can be the same or different and Z represents oxygen,

sulphur, or a group of formula =N,E; wherein E represents hydrocarbon as described above or an electron-withdrawing group; or

R^2 and R^3 together with the intervening nitrogen and carbon atom represent carbonyl (C=O), thiocarbonyl (C=S), imino (C=N,R^a), oximino (C=N,OR^a), or a 3- to 8-membered ring containing from zero to 4 hetero-atoms selected from the group consisting of oxygen, nitrogen, sulphur and phosphorus; wherein R^a represents hydrogen or hydrocarbon as described above;

wherein each of the R^2 and R^3 substituents can be the same or different; and

X represents halogen and each of the 5, 7, substituents can be the same or different.

13. A compound of claim 12 wherein each of the X substituents is chloro, R^1 is hydrogen, and R^2 and R^3 each is a phenyl group.

14. A compound of claim 12 wherein each of the X substituents is chloro, R^1 is an alkyl group having 1 to 3 carbon atoms, and R^2 and R^3 each is a phenyl group.

15. A compound of claim 12 wherein each of the X substituents is chloro, R^1 is hydrogen, one of R^2 and R^3 is an unsubstituted phenyl group and the other is phenyl having an alkoxy substituent having 1 to 3 carbon atoms.

16. A method of preparing a compound of claim 12 comprising the steps of:

a) reacting 3,5-dichloroaniline and dimethyl acetylenedicarboxylate to form dimethylanilinofumarate;

b) cyclizing the dimethylanilinofumarate with diphenyl ether to form 4(1H)-quinolone-2-carboxylate;

c) aminating the 4(1H)-quinolone-2-carboxylate with chlorosulphonyl isocyanate in acetonitrile to form a 4-aminated derivative thereof; and

d) acylating the 4-aminated derivative with diphenyl carbamoyl chloride to form (N,N-diphenyl)-4-ureido-5,7-dichloro-2-carboxy-quinoline methyl ester.